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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/357,704	07/20/99	BANDER	N 242/024

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EXAMINER	
HUNT, J	
ART UNIT	**PAPER NUMBER**
1642	6

DATE MAILED: 09/12/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/357,704	Bander
Examiner	**Group Art Unit**
Jennifer Nichols, Nee Hunt	1642

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-19 and 80* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-19 and 80* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4,5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Aknowledgement is made of applicant's cancellation of claims 20-67, and newly added claim 80. Claims 1-19 are pending in the application.

Claim Objections

1. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claim 80 been renumbered as claim 68.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 and renumbered claim 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-19 and renumbered claim 68 are unclear in the recitation of a "biological agent". The metes and bounds of a biological agent cannot be determined. It is not clear what would be considered a biological agent and what would not.

Claims 7-9 are unclear in the recitation "wherein an antibody is used in carrying out said method". It is not clear if "an antibody" refers to the same antibody recited in claim 2, or if "an antibody" recited in claim 7 refers to some other antibody in the instant method.

Claims 12-14 are unclear in the recitation of a "substance effective to kill or ablate". The metes and bounds of "substance effective to kill or ablate" cannot be determined. It is not clear what would be considered "substance effective to kill or ablate" and what would not, how said substances would be determined, or what qualities said substances would be characterized by

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 80 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 80 recites prophylactic treatment, which is not supported by the original disclosure as filed. This is a new matter rejection.

5. Claims 1-19 and 80 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The claims are broadly drawn to methods of ablating or killing normal, benign hyperplastic, and cancerous prostate epithelial cells, including in vivo therapy, and prophylactic methods of treatment.

The specification discloses 4 antibodies (E99, J415, J533, and J591) which were raised to the prostate cancer cell line LNcAP. The antibodies are shown to react strongly with prostate tissue and not normal tissue, and stain viable LNcAP cells. The J591 monoclonal antibody is shown to become internalized after binding viable LNcAP cells. Further, by immunoprecipitation, the antibodies are shown to bind identical bands as the PSMA specific antibody 7E11. Competition studies were performed between the new antibodies. Finally, the new antibodies were shown to bind to tumor vasculature in general in fixed tissue *in vitro* studies.

The specification fails to provide sufficient guidance and objective evidence to enable one skilled in the art to predictably kill or ablate cells, including *in vivo* treatment, using agents or antibodies that bind the extracellular domain of PSMA and target tumor vasculature. The PSMA antigen has been shown in the art to be specifically expressed in prostatic tissue. The instant demonstration that new antibodies E99, J415, J533, and J591 bind to vasculature in fixed tissue does not render it predictable that the new antibodies are binding to PSMA or that PSMA is expressed by vascular endothelial cells of tumors in general. The cell line used to raise the instant antibodies expresses tumor specific antigens which may not necessarily be prostate specific. While the new antibodies E99, J415, J533, and J591 recognize the same size band by immunoprecipitation as does 7E11, there is no direct objective evidence supplied that the antibodies are binding the same antigen. Competition studies are performed between the new antibodies to show they are, in the case of E99, J533, and J591, binding the same antigen, but the

7E11 antibody fails to block any of the new antibodies in competition studies, indicating that the antibodies at least bind different epitopes. This provides no evidence to confirm binding of the same antigen. While the antigen recognized by the antibodies E99, J415, J533, and J591 appears to be expressed in normal prostatic tissue, on LNcAP cells, and in tumor vasculature, there is insufficient objective evidence to render it predictable that the antigen is PSMA, and that the antibodies bind to normal, benign hyperplastic and cancerous prostate epithelial cells. Likewise monoclonal antibody J591 is shown to be internalized after binding to LNcAP cells, however since it is not predictable that the antigen bound is the extracellular domain of PSMA, it is also unpredictable and would require undue experimentation to bind agents to PSMA which are also internalized.

In addition, the specification provides evidence of the ability of the antibodies to target tissues *in vitro* for detection but provides insufficient objective evidence that antibodies to the PSMA extracellular domain, or the antibodies E99, J415, J533, and J591 effectively bind to normal, benign hyperplastic and cancerous prostate epithelial cells *in vivo*. Jain, R.K. et al., Cancer and Metastasis Reviews (IDS) teaches that the efficacy in cancer therapy of novel therapeutic agents such as monoclonal antibodies, cytokines, and effector cells has been limited by their inability to reach their target *in vivo* in adequate qualities. Three physiological factors responsible for poor localization of macro molecules in tumors have been identified: (I) heterogenous blood supply, (II) elevated interstitial pressure which lowers fluid extravasation, and (III) large transport distances in the interstitium. Furthermore, the average vascular surface

area decreases with tumor growth, hence reducing transvascular exchange in large tumors compared to smaller tumors. The molecule may also bind non-specifically to proteins or other tissue components, bind specifically to the target and/or be metabolized which further lowers the effective diffusion rate by reducing the amount of mobile molecule. Finally, although the effector cells are capable of active migration, peculiarities of tumor vasculature and interstitium may also be responsible for poor delivery. Furthermore, it is well known in the art that the therapeutic effectiveness of immunotoxins is unpredictable. Generally, an effective therapeutic protocol for the treatment of a tumor, or the killing of cells in general is subject to a number of factors beyond simply the binding of a specific antibody to the marker antigen. Demonstration of antigen specificity in vitro cannot alone support operability for the method of killing of cells, including tumor cells, and prophylactic treatment of prostate cancer through administration of the antibody or antibody conjugates. In addition to the factors discussed previously, antigenic variables, such as intensity of antigen expression, heterogeneity of antigen expression, the chemical nature, location, and accessibility of the target antigen, as wells as antibody variables such as clearance mechanisms and persistence in tissues affect the outcome of *in vivo* based antibody methods.

Thus, the demonstration of in vitro binding to tissue samples provides insufficient objective evidence that the instant antibody-toxins are predictably effective in ablating or killing cells in the in vivo clinical situation, based on in vitro binding to cells. Indeed, there is not

indication that binding of J591 antibody to live LNcAP cells had any effect on their viability. The specification does not teach how to extrapolate data obtained by the immunohistochemical assays to the development of effective in vivo mammalian therapeutic methods commensurate in scope with the claimed invention.

Furthermore, applicant has provided no evidence that the new antibodies bind to prostate tissue in vivo. As set forth above, *in vivo* antibody methods are unpredictable and generally lack correlation to *in vitro* results due to physiological, antigenic, and other factors. Therefore, absent evidence, it is not clear that the new antibodies would bind to any prostate material *in vivo*, and even if they did bind *in vivo*, it is not clear what they would bind to, or if said binding would be useful for cell killing or prophylactic treatment. Therefor it is not clear that a skilled artisan could predict the efficacy of the administration of agents or antibodies which bind the extracellular domain of PSMA to ablate or kill prostate cells based on the disclosure in the specification.

Therefor one of ordinary skill in the art would not have been enabled to practice the full scope of the invention as claimed.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Nichols, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Nichols, Nee Hunt

September 11, 2000

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